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RAPID RECOMMENDATIONS

Summary of WHO clinical practice guidelines for influenza

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ABSTRACT

ABOUT THIS GUIDELINE

This *BMJ* Rapid Recommendation is a summary of a World Health Organization guideline published 12 September 2024. The full guideline is available in MAGICapp and in PDF on the WHO website. The WHO guideline is primarily for healthcare providers and takes a patient-centred perspective on benefits and harms. Other considerations include resource implications, acceptability, feasibility, equity, and human rights of relevance to healthcare systems. Recommendations were developed according to standards and methods for trustworthy guidelines by a panel of non-conflicted experts, as delineated in the WHO handbook (<https://www.who.int/publications/i/item/9789241548960>).

CLINICAL QUESTIONS

What is the role of medications in treating non-severe and severe influenza including zoonotic disease (novel influenza A), and in preventing infection among contacts? Which diagnostic testing strategies best enable rapid and accurate treatment decisions?

CONTEXT AND CURRENT PRACTICE

New randomised controlled trial (RCT) evidence, ongoing concerns about zoonotic disease, and the increasing availability of rapid diagnostic tests require updated guidance.

RECOMMENDATIONS

apply to seasonal influenza and zoonotic influenza. There are 29 recommendations; 21 related to antiviral medications and six to adjunctive therapies to prevent and treat influenza. Recommendations are stratified by severity of disease and risk of disease progression. For seasonal influenza, WHO conditionally recommends treatment within 48 hours of symptom onset with oseltamivir for severe illness, and baloxavir for patients at high risk of progression from non-severe to severe illness. WHO also conditionally recommends prophylaxis (using baloxavir, laninimavir, oseltamivir, or zanamivir) for anyone exposed to zoonotic influenza, and for those exposed to seasonal influenza who are at extremely high risk. The panel issued recommendations against the use of adjunctive therapies in patients with non-severe influenza (strong recommendation against antibiotics) and severe influenza (conditional recommendation against corticosteroids, macrolides, mTOR inhibitors, non-steroidal anti-inflammatory drugs, and passive immune therapy). A recommendation is made for diagnostic testing strategies in non-severe and severe influenza disease.

THE EVIDENCE

Four systematic reviews of RCTs provided low to very low certainty evidence on benefits and harms of

antiviral medications and adjunctive therapies. A systematic review of prognostic factors provided baseline risk estimates and information on individual risk factors for disease progression. A decision analysis model informed recommendations for testing based on alternative potential diagnostic pathways. Influenza viruses cause an estimated annual one billion cases of acute respiratory disease including 3-5 million severe cases and 290 000-650 000 deaths.^{1,2} Clinical management involves supportive and symptomatic care, with specific therapy directed by reliable identification of those with severe disease and those at high risk of developing severe disease. Differentiation from other viral and bacterial infection requires diagnostic testing; reference standard, RNA-based testing of respiratory specimens is far from universally accessible, although less sensitive and specific rapid diagnostic tests are increasingly available.

Randomised controlled trial (RCT) evidence for therapeutics continues to evolve, including new potential antiviral treatments.³ Neuraminidase inhibitors (NAIs) have in vitro activity against seasonal influenza virus A and B and zoonotic influenza A.^{4,5} Oral oseltamivir is the most widely studied and available. Others include inhaled laninamivir, intravenous peramivir, and inhaled zanamivir. Alternatively, baloxavir, a selective inhibitor of influenza cap-dependent endonuclease which can be administered as a single oral dose, has been approved in some jurisdictions for early treatment of paediatric and adult patients with uncomplicated influenza.⁶

The purpose of this article is to provide a summary of the WHO guideline published on 12 September 2024.⁷ This WHO guideline replaced a previous version from 2022.⁸ It includes recommendations on antivirals and immunomodulators for treatment of patients with influenza disease, and on chemoprophylaxis for people exposed to influenza virus. It also includes recommendations for the use of diagnostic tests for patients presenting to primary care, emergency departments, or equivalents with influenza-like illness. [Box 1](#) gives linked resources, including the full guidelines and the evidence informing the recommendations. These systematic reviews and the modelling study were commissioned by the WHO to explicitly answer the questions defined by the WHO guideline panel.

Box 1: Linked resources in this *BMJ* Rapid Recommendations cluster

Full WHO guideline

- MAGICapp: <https://app.magicapp.org/#/guideline/9184>
- WHO portal: <https://www.who.int/publications/i/item/9789240097759>

Evidence informing the guideline

- Two systematic reviews and network meta-analyses on antivirals for treatment of severe and non-severe influenza patients^{9 10}
- Updated systematic review on adjunctive immunomodulator treatments for treatment of patients with severe influenza¹¹
- Systematic review of antivirals for prophylaxis for persons exposed to seasonal or zoonotic influenza viruses¹²
- Systematic review of observational data on prognosis which provided baseline risk estimates for hospital admission and death in patients with non-severe and severe influenza virus infections, including those with seasonal and zoonotic influenza A viruses associated with high mortality in humans.¹³ This review also informed an updated list of independent risk factors associated with severe disease and mortality.
- Updated decision making model for diagnostic strategies for caring for patients with influenza virus infection (see Annex 2 in the full guideline)

This guideline contributes to the *BMJ* Rapid Recommendations series, which provides clinicians with trustworthy recommendations for potentially practice-changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between MAGIC and *The BMJ*.

Key issues to consider when applying the recommendations

WHO definitions of influenza severity

This guideline applies to adults and children with influenza virus infection and those who are exposed to influenza viruses, irrespective of vaccination status. Recommendations differ based on the severity of influenza, according to WHO criteria. The systematic review of prognosis studies¹³ informed baseline risk estimates for hospital admission and death as well as individual risk factors associated with these outcomes:

- Non-severe influenza* reflects the absence of any manifestation of severe disease and may include sudden onset of cough, headache, muscle and joint pain, severe malaise, sore throat,

and rhinorrhea, with or without fever. Most people recover symptomatically within a week without requiring medical attention.

- Severe influenza* typically requires hospital admission and may include severe pneumonia, sepsis, septic shock, acute respiratory distress syndrome, multi-organ failure, and/or exacerbation of chronic medical conditions. Severe illness may, in some cases, require supplemental oxygen, invasive or non-invasive ventilation, and/or vasopressor therapy.

Disease caused by novel influenza A associated with high mortality or with an unknown risk of severe disease, is considered severe even if in the absence of the above criteria.

How to identify patients with non-severe influenza at high risk of hospital admission

Several recommendations pertain only to patients at elevated risk for severe disease (hospital admission). The systematic review of prognosis studies identified major risk factors and baseline risk estimates for hospital admission, as well as for mortality.¹³ Those considered high risk have at least one major risk factor defined as an odds ratio >2.0 (that is, which increase the odds of hospital admission at least twofold): age of 65 years or older, immunocompromising conditions, cardiovascular disease, neurological disease, and chronic respiratory disease. Baseline risk of hospital admission in these patients was estimated to be 21 per 1000 (2.1%). Patients considered extremely high risk include those aged 85 years or more, and those at any age with multiple (two or more) major risk factors.

Novel influenza A (zoonotic influenza) is associated with a high risk of mortality in humans and is considered severe disease even in the absence of risk factors. This includes infection with HPAI A(H5N1), HPAI A(H5N6) and HPAI and LPAI A(H7N9) viruses.

What is a conditional recommendation?

Most recommendations in this guideline are “conditional” in their strength. A conditional recommendation means the same as a “weak recommendation” (used in other *BMJ* Rapid Recommendations) with identical implications for practice. [Table 1](#) provides interpretations of strong and conditional recommendations from the perspectives of patients, clinicians, and policy makers.

Table 1 | Strength of recommendations and implications

Implications for...	Strong recommendation “We recommend....”	Conditional recommendation “We suggest....”
Patients	All or almost all people in this situation will want the recommended course of action and only a few will not	The majority of people in the situation would want the recommended course of action, but a substantial minority would not (or vice versa). Shared decision-making should be emphasised
Clinicians	All or almost all patients should be prescribed the recommended course of action (or vice versa).	Different choices will be appropriate for different patients. Patients will need help to arrive at a management decision consistent with their values and preferences, with shared decision-making as an appropriate way to achieve this goal.
Policy makers	The recommendation could be adopted as policy.	There is a need for substantial debate and involvement of stakeholders.

In this guideline (as further detailed in [box 2](#) and the methods section of the full guideline⁷), the WHO guideline panel considered the magnitude of benefits and harms, the certainty of evidence (high to very low) supporting estimates of the magnitude of benefits and

harms, and their assumptions regarding values and preferences of stakeholders (in particular, patients infected by influenza virus).

Box 2: How the guideline was created (see full guideline⁷ for details)

Standards, methods, and processes for trustworthy guidance

This WHO guideline update is aligned with the WHO Handbook for guideline development, and guided by a planning proposal pre-approved by the WHO Guideline Review Committee (GRC).¹⁴ The GRADE approach provided the framework for evaluating certainty of available evidence and for moving from evidence to recommendations. The guideline was initiated in 2022 and made publicly available on 12 September 2024, following GRC approval. After publication, the WHO requested support from MAGIC Evidence Ecosystem Foundation to create a summary of the full guideline as a *BMJ* Rapid Recommendations publication.

Who was involved?

WHO recruited an international guideline panel including patients (individuals with lived experience), technical experts in influenza, researchers, and clinicians. See the full guideline (box 2) for details. They included an expert in health ethics, recognising the challenges of providing recommendations that take into account large variation in global health systems' capacity and capability. Members were balanced by geography, gender, and expertise. The panel collectively determined the scope of this guideline and developed recommendations. Methods and clinical co-chairs were selected by the WHO to lead panel deliberations. There were no reported financial conflicts of interest. Intellectual conflicts of interest were minimised, managed, and are reported as supplementary material.

What research did the guideline panel request and review?

The panel defined the clinical questions and related population, intervention, outcomes, and subgroups of interest to be addressed by the guideline. Pre-specified teams conducted four parallel systematic reviews of randomised trials on the medications of interest to answer these questions, under WHO oversight (see box 1). To ensure that the reviews were fit for purpose, some review authors were also guideline panel members, and none declared important conflicts of interest.

To understand the prognosis of patients with influenza, particularly those with non-severe illness and their risk of progression to severe illness, an independent team of researchers systematically reviewed available observational data regarding the prognosis of patients with both non-severe and severe influenza, and risk factors for disease progression (see box 1).

Regarding diagnostic testing strategies, the panel anticipated finding no observational studies or randomised trials directly comparing influenza testing strategies, and therefore recommended a modelling approach. An independent team of methodologists developed a decision analytic model based on data from a recent meta-analysis to assess the optimal strategy for influenza testing and linkage to treatment quality-adjusted life days (QALDs).

Guideline perspective, outcomes, and minimally important benefits

The guideline panel took an individual patient perspective in making recommendations but also considered resource implications,

acceptability, feasibility, equity, and human rights of relevance to healthcare systems.

Among the patient-important outcomes initially selected and prioritised by the panel, trial evidence for therapeutic benefit was largely confined to length of hospital stay and duration of illness. These outcomes, weighed against generally limited adverse events, therefore drove the recommendations.

Key to decision making were the thresholds of importance that the panel inferred for each outcome of importance (minimally important differences (MID)). In the absence of identified empirical evidence, these thresholds were pragmatically determined from a structured survey of panel members, resulting in an MID of 1 day for hospital stay and illness duration (see full guideline for more details).

How were values and preferences of patients incorporated?

In the absence of a systematic review regarding the values and preferences of adults with influenza virus infections, the guideline panel relied on their own judgment of what well informed patients would value after carefully balancing benefits, harms, and burdens of therapy. The panel agreed that the following values and preferences would be typical of well informed patients:

- "Most patients would choose to use a medication that had a small but important effect on outcomes they consider important, provided that there is a low likelihood of adverse effects, and that adverse effects when they do occur are mild."
- "Most patients would be reluctant to use a medication in which there was considerable uncertainty regarding its benefits and would only do so if the low certainty evidence suggested a benefit, there was a low likelihood of adverse effects, and that adverse effects when they did occur were mild"

In addition to these considerations, the panel inferred that convenience versus burden were important to patients. For instance, single oral dose baloxavir would be appealing compared with more complex dosing regimens.

The main reason why the strength of most recommendations was conditional in this guideline was due to a fine balance of benefits and harms in combination with low or very low certainty evidence.

Recommendations

The infographic summarises the recommendations in favour and against the use of antiviral medications. These are conditional in strength due to evidence of low or very low certainty for potentially small benefits and low likelihood of adverse effects (see table 1 for implications).

Rapid recommendation: Influenza

Clinical practice guideline on treatment and prophylaxis

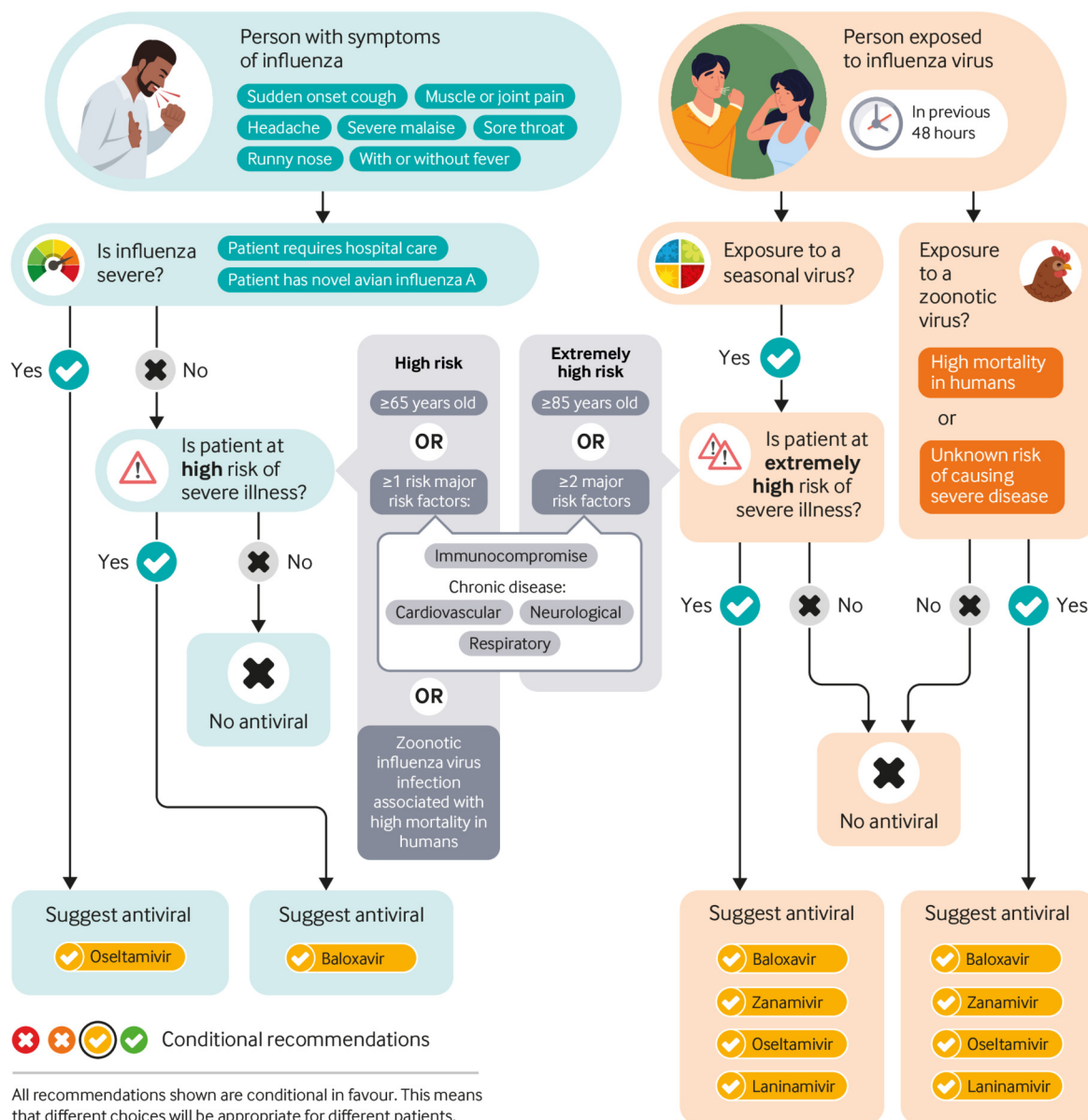
See full guideline for recommendations on adjunctive therapies and diagnostics

MAGIC app

See more details of recommendations and evidence base



Guidelines from the World Health Organisation suggest different antiviral treatments depending on disease severity, risks of developing severe disease, and exposures. This graphic outlines conditional recommendations in favour of antiviral treatments. However because of small benefits and uncertainty of the evidence, there are no strong recommendations in favour of any treatment. More information about conditional and strong recommendations against treatments can be found on the MAGICapp website using the links on this page



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The full guideline provides all 29 recommendations. These include recommendations on antiviral treatment and prophylaxis, adjunctive therapies, and diagnostic testing strategies. All treatment recommendations are based on systematic reviews, whereas diagnostic strategies are based on an updated decision model

(Annex 2 in the full guideline⁷). These reviews and the decision model were commissioned by the WHO.

The accompanying infographic summarises 21 recommendations; six additional recommendations against adjunctive therapies and

two recommendations for diagnostic testing strategies not captured in the infographic are summarised below:

- For *adjunctive therapies*, WHO issued a strong recommendation against the use of antibiotics in patients with non-severe influenza with low probability of bacterial co-infection. WHO also issued conditional recommendations against adjunctive immunomodulatory therapies for patients with severe influenza, including corticosteroids, macrolides, mTOR inhibitors, non-steroidal anti-inflammatory drugs, and passive immune therapy.
- For *diagnosing patients with suspected seasonal influenza*, WHO issued a conditional recommendation for the use of nucleic acid amplification test (NAAT) or polymerase chain reaction (PCR) testing for patients with suspected severe influenza and a

conditional recommendation for use of digital immunoassay (DIA) or NAAT for patients with suspected non-severe influenza who are at high risk of progression to severe influenza.

The full guideline provides complete recommendation statements with critical remarks, GRADE evidence summaries based on systematic reviews (box 1) and decision aids, practical information, and justifications made by the WHO.⁷ The guideline is available in multilayered digital formats through an online platform (<https://app.magicapp.org/#/guideline/9184>). Figure 1 gives an example of a conditional recommendation for the use of baloxavir in patients with non-severe influenza and at high risk of progression to severe influenza. Practical information underscores the need to give the drug within 48 hours of symptom onset, and details dosing considerations where relevant.

Conditional recommendation for

Benefits outweigh harms for the majority, but not for everyone. The majority of patients would likely want this option. [Learn more](#)

In patients with suspected or confirmed non-severe influenza virus infection and at high risk of progression to severe influenza, we **suggest administering baloxavir** (conditional recommendation, low-quality evidence).

Patients with non-severe influenza and at high risk of developing severe disease include the following (see Sections 5.1 and 5.2):

- Patients 65 years and older; or
- Patients with one or more major risk factors for severe influenza.

Patients with zoonotic influenza virus infection associated with high mortality in humans, including HPAI A(H5N1), HPAI A(H5N6) virus; and HPAI and LPAI A(H7N9), were not included in the clinical trials that informed this recommendation. The GDG agreed that evidence would indirectly apply to this population as well, in case they would present early to care with mild symptoms.

Treatment should be administered as early as possible, and within 2 days of symptom onset.

Research evidence (1) Evidence to decision Justification **Practical info** Decision Aids References Feedback

Route, dosage and duration

Baloxavir is given orally as a **single dose**, based on body weight, as below.

Body weight	Dose of baloxavir
< 20 kg	2 mg/kg (as suspension)
20 kg to 79 kg	40 mg (tablet)
80 kg and over	80 mg (tablet)

Treatment should be administered as early as possible, and within 2 days of symptom onset.

Fig 1 | Example of multilayered guideline recommendation in the WHO *Clinical practice guidelines for influenza*⁷

Applying recommendations

Recommendations provided need to be contextualised to real-world clinical practice. We present clinical vignettes illustrating some of the recommendations provided by the WHO in this guideline.

Clinical vignette—A 78 year old woman attended her primary care facility on her second day of symptoms. She has a fever, body aches and a sore throat, but no cough. She felt slightly more breathless than usual this morning, but arrived at the polyclinic on public transport. She has mild coronary artery disease which is appropriately treated, and experienced no recent angina. She has no contact with animals, and lives with her younger husband who is in good health. Several close friends were ill last week with similar

symptoms. On examination, her oxygen saturations are 98%, and other vital signs are normal. There are no focal respiratory signs on examination. With suspected non-severe influenza in a patient at high risk of hospital admission (given her age and presence of ischaemic heart disease), a swab (digital immunoassay) was taken by the assessing doctor for molecular point-of-care influenza testing in the surgery, which was positive for influenza A. Other routine tests were taken.

The patient was prescribed baloxavir 80 mg single oral dose immediately for her non-severe influenza. Teleconsultation over the next five days showed that initial worsening of myalgia and headache was not associated with any symptoms that would require hospital admission. Other blood tests returned normal, and her

symptoms began to improve on day three after consultation. Her husband, being a close contact but not having any factors associated with extremely high risk of severe illness, was not given chemoprophylaxis.

Clinical vignette—A 62 year old woman presents to primary care within 36 hours of symptom onset. Presenting symptoms include a fever, cough, myalgia, and malaise during a period of known seasonal influenza circulation. She has well controlled hypertension but no other major comorbidities. She seems clinically stable, with normal oxygen saturation and no obvious signs of pneumonia.

In this setting, the clinician first assesses illness severity and risk of progression. Given the absence of severe disease features and no major risk factors, testing may not alter immediate management, which is likely to consist of watchful waiting, symptomatic care, and advice regarding when to return to seek care.

Clinical vignette—By contrast, a 78 year old man presenting to the emergency department with dyspnoea, hypoxia, hypotension, and bilateral infiltrates on chest imaging during influenza season meets the criteria for severe influenza. In this setting, the guideline conditionally recommends NAAT or PCR testing to support timely antiviral treatment and appropriate escalation of care. Given suspected severe influenza virus infection, the clinician should consider initiating a five day course of oseltamivir, ideally within 48 hours of symptom onset, in consultation with the patient through a shared decision making process.

Uncertainties and future research

There is a need for a better evidence based understanding of patients' values and preferences. Other key areas of uncertainty where more evidence is needed are summarised in the full guideline,⁷ and encompass medications for which only low certainty evidence exists regarding benefits and/or harms, and modelling of outcomes for diagnostic strategies. Evidence is also lacking on key groups, including children, immunocompromised patients, and pregnant women. Safety data for baloxavir is an important priority.

Research networks should adopt efficient designs for generating evidence, including the use of "always-on platforms" (versatile research platforms, which can rapidly pivot to answer questions that arise), particularly for severe disease, and maximising the harmonisation of research protocols to allow patient-level data to be meta-analysed appropriately.

How patients were involved in the creation of this article

The panel included one patient with lived experience of influenza virus infection. Recognising this limitation in patient involvement, the WHO also allowed guideline panel members with direct personal experience of influenza to contribute with their perspectives while recognising limitations in considering the values and preferences associated with decision making.

Competing interests: Declarations of interest and biographies of the WHO guideline panel members are available at [https://cdn.who.int/media/docs/default-source/health-care-readiness/vs-19-oct-influenza-gdg-bios-\(1\).pdf](https://cdn.who.int/media/docs/default-source/health-care-readiness/vs-19-oct-influenza-gdg-bios-(1).pdf). No panel member was judged by the WHO to have important conflicts of interest.

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WHO would like to thank the collaborative efforts of all those involved in making this guideline, as detailed in the full guideline.¹¹ The WHO and the authors of this paper thank Helen MacDonald of *The BMJ* for her input in making this summary version of the guideline more accessible and understandable for frontline clinicians.

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